ETS

Residential Radon and Lung Cancer among Never-Smokers in Sweden

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In this study, we attempted to reduce existing uncertainty about the relative risk of lung cancer from residential radon exposure among never-smokers. Comprehensive measurements of domestic radon were performed for 258 never-smoking lung cancer cases and 487 never-smoking controls from five Swedish case-control studies. With additional never-smokers from a previous case-control study of lung cancer and residential radon exposure in Sweden, a total of 436 never-smoking lung cancer cases diagnosed in Sweden between 1980 and 1995 and 1,649 never-smoking controls were included. The relative risks (with 95% confidence intervals in parentheses) of lung cancer in relation to categories of time-weighted average domestic radon concentration during three decades, delimited by cutpoints at 50, 80, and 140 Bq m^{-3}, were 1.08 (0.8–1.5), 1.18 (0.9–1.6), and 1.44 (1.0–2.1), respectively, with average radon concentrations below 50 Bq m^{-3} used as reference category and with adjustment for other risk factors. The data suggested that among never-smokers residential radon exposure may be more harmful for those exposed to environmental tobacco smoke. Overall, an excess relative risk of 10% per 100 Bq m^{-3} average radon concentration was estimated, which is similar to the summary effect estimate for all subjects in the main residential radon studies to date. (EPIDEMIOLOGY 2001;12:396–404)

Keywords: case-control study, lung neoplasms, risk assessment, radon, never-smokers, cocarcinogenesis, tobacco smoke pollution, environmental exposures.

Inhalation of radon is the main source of exposure to radioactivity in the general population of most countries.[1] Radon concentrations can be markedly increased indoors because air space is confined, exchange with outside air is limited, and lower air pressure in buildings favors penetration of radon from the soil.[2] Exhalation from radium-rich building materials, used in about 10% of the Swedish housing stock, and release of radon dissolved in water can also in some circumstances contribute to indoor radon levels. Radon gas decays into short-lived products emitting high-energy alpha particles that irradiate the bronchial epithelium after inhalation and deposition.[3]

Numerous epidemiologic studies have been conducted to quantify the association between lung cancer and radon exposure both in occupational settings, such as among miners, and in the general population. Epidemiologic studies of residential radon provide effect estimates based on levels experienced by the general population and thereby avoid the extrapolation from high to low exposure levels that occurs when effect estimates are obtained from miner studies. Nevertheless, the overall patterns of risk ratios in the two settings show good agreement and support an excess lung cancer risk with increased levels of radon exposure.[4–6] Experimental animal studies show that interaction with other environmental agents is not necessary for the induction of lung cancer by radon, but the experimental exposure rates are not commensurable with average levels in dwellings.[7]

An important issue, which requires further clarification, concerns the risk posed by radon for never-smokers. The miner data suggest a steeper increase in relative risk with radon exposure among never-smokers than among smokers.[4] By contrast, the summary exposure-response estimates from meta-analyses of residential radon studies appear similar with and without restriction to subjects who never smoked, respectively, although the effect estimate among never-smokers is uncertain owing to few lung cancer cases.[5] Results among miners have been more influential for risk assessment than those conducted in the general public, although inference about never-smokers is also limited, as it relies on a total of only 64 cases of lung cancer in miner studies.[4,8] The present work aims to strengthen the evidence re-

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garding the radon-related lung cancer effect among never-smokers in the general population. In addition, we investigate for the first time the interaction between exposure to environmental tobacco smoke (ETS) and residential radon in relation to lung cancer.

Subjects and Methods

STUDY DESIGN

The database for never-smokers in five case-control studies (individually described below) was complemented with measurements of radon concentrations in dwellings occupied during the retrospective 32-year period ending 3 years before assessment of disease status (hereafter referred to as the observation period for radon exposure). These studies were originally conducted for purposes of evaluating the association of lung cancer with environmental and occupational exposures other than radon. The subjects from these studies were analyzed here with respect to radon exposure for the first time and were combined for additional analyses with the never-smokers from a previous study of residential radon exposure and lung cancer in Sweden. All never-smoker case subjects in participating studies were included provided that their year of diagnosis was 1980 or later. A subject who had not smoked daily for 1 year or longer was defined as a never-smoker. We selected up to twice as many never-smoker control subjects, matched on birth year (up to a 3-year difference), sex, and study, as case subjects. The date of diagnosis for a case determined the end of follow-up for the case subject and his or her matched controls. For some controls, their own date of death marked their end of follow-up, if death occurred before (up to 3 years) the diagnosis of the matched case. These instances occurred for Study 2 (below), in which controls had been originally frequency-matched to the cases on age at calendar year of diagnosis, using 5-year age groups, and for Study 3, in which controls had been originally frequency-matched to the cases on time period for occurrence of death. Such corrections for the date of end of follow-up among controls were also necessary among the other studies but only on the level of months.

Radon Exposure

We obtained the addresses for the residences occupied by study subjects for at least 2 years during the observation period for radon exposure through parish registers, as a complement to the residential history that was also obtained from questionnaires in most of the participating studies. Measurements of radon concentrations were performed during the heating season, that is, between October and May, in 1996/1997 and 1997/1998, using two detectors per dwelling placed for 3 months in the bedroom and the living room. The detectors were placed and collected by qualified public health officers and were processed at the Swedish Radiation Protection Institute. A detector consists of a holder containing an alpha-track detector material, CR-39 (allyl diglycol carbonate), and the track density of the film is measured by an automatic film reader after chemical etching.[9] For each address, the radon concentration was estimated by the average of the measured radon levels in bedroom and living room.

The length of the observation period for radon exposure was 32 years, except for 11 subjects younger than 35 years of age at the end of follow-up. The time-weighted average (TWA) radon concentration for a study subject during the observation period was based on radon concentrations over all addresses occupied by the subject during that time period, weighting concentrations proportionally to the number of years spent at each address. For the time intervals for which no measurement was available, we imputed the study-specific arithmetic average of radon concentrations for measured addresses of control subjects.[10] For the supplementary data from the nationwide Swedish study described below, averages of measured addresses among controls were estimated for three groups of municipalities classified according to radon risk and used for imputation of unmeasured addresses within corresponding groups.[10]

Other Risk Factors

Unless data had already been collected by the contributing study, information on ETS exposure was obtained through telephone interview of study subjects or proxies, using a questionnaire containing questions about domestic exposure to ETS during adulthood, including intensities and time periods of smoking by spouse or cohabitant. Subjects were classified into one of four categories according to whether they had ever been exposed to ETS at home and whether the lapse of time since last exposure to ETS was equal to or larger than 15 years, between 15 and 3 years, or less than 3 years. Such classification appeared to be more appropriate for relating the excess risk of lung cancer to ETS exposure than the simple dichotomy ever-/never-exposed.[11]

Two dichotomous variables for occupational lung cancer risk were constructed. One variable distinguished subjects who, for a year or more during their whole occupational history, had held occupations recognized to present lung cancer excess risk, whereas the other variable distinguished subjects who had held occupations suspected to present lung cancer excess risk.[12,13] Classification relied on Scandinavian occupational codes (NYK-83)[14] and, for Study 1 (below), on the cross-classification of international occupational (ISCO-68) and industrial codes (ISIC-71).[13]

We constructed a socioeconomic indicator variable with four levels by combining two dichotomies indicating whether, on a TWA basis, the jobs reported in the working history predominantly required short or long education and manual work or not.[15]

We constructed a dichotomous variable for urbanization by distinguishing subjects who lived for 10 years or more in one of the three largest cities in Sweden (Stockholm, Göteborg, or Malmö) at some time during the follow-up period.

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SUMMARY OF DATA SOURCES

Study 1

The relation between ETS exposure and lung cancer was investigated among never-smokers, 30 years of age or older, residing in Stockholm County.[11] Cases were recruited between October 1, 1989, and September 30, 1995, among patients referred to the three main hospitals responsible for medical investigation and treatment of lung cancer in this area. All suspected lung cancer cases were screened for smoking status, and all never-smokers were traced until they either were included in the study when diagnosed as having lung cancer [*International Classification of Diseases* (ICD), 9th revision, code 162] or were excluded. About twice as many controls were frequency-matched to the case subjects by age group (30–49, 50–69, and 70 years and older), sex, and hospital catchment area. Interviews were conducted in person or by telephone using a detailed questionnaire on exposure to ETS, occupational and residential histories, and other relevant exposures. Answers regarding never-smoking status and ETS were validated through a secondary interview with a next-of-kin.[16] The participation rate was 85.5% among cases and 82.9% among controls screened for never-smoking status (6.1% of controls potentially eligible as never-smokers could not be contacted even for screening). All 124 cases and 235 controls were selected for the present study. The basis for diagnosis was tissue histology for 79.0% and cytology for 20.2% of the case subjects.

Study 2

With the primary aim to clarify the relation between environmental or occupational air pollution and lung cancer, a case-control study was conducted among men 40 to 75 years of age and resident in Stockholm County at some time between January 1, 1985, and December 31, 1990, and with no more than 5 years of residence outside of the county between 1950 and 1990.[15,17] A total of 1,196 eligible cases were identified, using the Stockholm County regional cancer registry, among cases of lung cancer (ICD-7, code 162.1) diagnosed between January 1, 1985, and December 31, 1990. About twice as many control subjects, frequency-matched to the cases on age at calendar year of diagnosis (in 5-years age groups), were randomly selected in 1992 from population registers of Stockholm County for the corresponding years. About half of the controls were additionally frequency-matched to the cases on vital status by 1990, using the Cause-of-Death Registry, excluding those with a smoking-related cause of death. A questionnaire was mailed to subjects or their next-of-kin, including questions about smoking, ETS exposure at home, and occupational and residential history, and was followed by phone contact. Among the 1,196 cases, and the 1,324 and 1,441 eligible controls matched and not matched for vital status, the participation rates were 87%, 82%, and 88%, respectively. All 33 never-smokers with lung cancer and twice as many controls were selected for the present study. The basis for diagnosis among never-smoker cases was tissue histology or cytology in 81.8% and 18.2%, respectively.

Study 3

A case-control study designed to assess the excess risk of lung cancer related to environmental emissions from Rönnskärsverken, a large smelting plant in northern Sweden, recruited cases and control subjects among men and women who had died in Skellefteå Municipality between 1961 and 1990, excluding those who had worked at Rönnskärsverken or as miners.[18] Subjects with a diagnosis of lung cancer (ICD-7, code 162) were identified using the Regional Cancer Registry and the National Cause-of-Death Registry. Twice as many controls, matched to cases on birth year and sex, were selected from the National Cause-of-Death Registry. A questionnaire about smoking habits, occupations, and residential history was mailed to next-of-kin and was often complemented by telephone interviews. The response rate for the 378 lung cancer cases identified was 94%, and about 93% for controls. For the present study, 78 never-smoking control subjects and 40 never-smoking cases diagnosed in 1980 or later were selected. The basis for diagnosis for these never-smoking cases was tissue histology or cytology for 70.0% and 30.0%, respectively.

Study 4

A case-control study, undertaken to investigate the relation between environmental factors and lung cancer, was conducted among subjects less than 75 years of age and living at the time of the study in one of 26 municipalities in Gothenburg and Bohus County and Älvsborg County, in southwest Sweden.[19] The municipalities were selected to represent the referral area of the three main regional hospitals where cases were recruited between January 1989 and June 1994, with occasional interruptions, among patients with suspected lung cancer referred to the pulmonary units. Potential cases and controls were matched for county, sex, and birth date by selecting controls registered on date of birth next to the cases within population registers. Interviews using a questionnaire to assess smoking, ETS, occupational exposures, and more were conducted in person, with a participation rate of 86% among cases and 75% among controls. Only suspected cases later diagnosed and recorded in the Regional Cancer Registry as having primary lung cancer (ICD-7, code 162.1) were retained (52%). Of the resulting 539 cases, all 49 never-smoker cases and twice as many never-smoker controls were selected for the present study. The basis for diagnosis was tissue histology or cytology for 87.8% and 10.2% of the cases, respectively.

Study 5

A case-control study was designed to investigate the association between occupational exposure and lung cancer. The study was conducted in a Swedish county, Västernorrland, containing a large number of paper and pulp mills. Cases were men diagnosed with primary lung cancer (ICD-7, code 162.1) between 1978 and 1991 reported to the Regional Cancer Registry in Umeå and

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deceased before September 1, 1992. Deceased controls were selected from the National Cause-of-Death Registry and matched to cases on year of birth, year of death, and municipality of residence at the time of diagnosis of the matched case. Subjects with suicide and lung cancer as cause of death were not accepted as controls. For each case not over 80 years of age at the time of the investigation, an additional living control, matched on year of birth and municipality of residence at the time of diagnosis of the case, was selected from the national population register. Information on occupational history and smoking habits was obtained through a questionnaire mailed to the study subjects or their next-of-kin. Participation rates were 88% among cases and 84% among controls. Among the resulting 562 cases and 878 controls, all 25 never-smoker cases, diagnosed in 1980 or later, and twice as many controls were included in the present study. The basis for diagnosis for the never-smoker cases was tissue histology or cytology for 76% and 24%, respectively.

Additional Data

Complementary analyses were performed using data from the nationwide Swedish case-control study for which the radon measurement procedures were similar.[20] This study included 1,360 cases of primary lung cancer (ICD-7, code 162.1) 35–74 years of age, diagnosed from 1980 to 1984, and 2,847 population controls. For eligibility, subjects had to live in Sweden on January 1, 1947, and had to reside at the time of selection in 1 of 109 municipalities that were regarded likely to be either low- or high-radon areas. In one group of controls, subjects sampled from the study base were frequency-matched for age (5-year intervals) and calendar year to the lung cancer cases. In another group, control subjects were additionally matched on vital status to the cases, excluding smoking-related causes of death. Radon was measured in 8,992 dwellings, and a measurement could not be obtained in 3,402 dwellings (27.4%), usually because the house no longer existed or was now being used only during summer. Information on potential risk factors for lung cancer was obtained from study subjects or next-of-kin through questionnaires supplemented by telephone interviews. The response rate was 82.2% for cases and 81.7% for controls. After selection of all never-smokers with at least one radon measurement within the 32-year observation period, data on 178 cases and 1,162 controls were available. The basis for diagnosis was tissue histology or cytology for 80.3% and 18.5% of the never-smoking cases, respectively.

Statistical Analysis

The data were analyzed using the Stata and Epicure statistical packages.[21,22] We estimated the excess relative risk (ERR) of lung cancer per unit of TWA residential radon concentration in conditional logistic regression analyses using a continuous variable for the TWA radon concentrations in dwellings of individual subjects. The 95% confidence limits for the ERR were based on the likelihood-ratio criterion.[23,24] A linear relative risk (*RR*) function was fitted to the data, $RR = 1 + \beta x$, where β is the ERR parameter and x denotes TWA residential radon level.[25,26] Maximum likelihood estimates of relative risks for categories of TWA residential radon level were obtained for categories delimited by cutpoints used in the nationwide Swedish study.[20] The indicator variable used for building the conditioning strata in the logistic regression model represented study, age group (5-year intervals), sex, and matched area of current residence, and to adjust further the effect of radon exposure, we added as predictors in the model indicator variables for ETS exposure, urbanization, occupational lung cancer risk, and socioeconomic status. Building these conditioning strata involved post hoc stratification because the original matching had sometimes matched never-smoking case subjects with smoking control subjects. For these subjects the matching was broken and reconstructed with never-smoking controls with corresponding levels of the matched factors. Given similar levels of the matching factors, the information on which controls and cases had been matched originally or in a second stage is irrelevant for the purpose of matching. In addition, individually matched pairs can be split to perform more valid analyses that condition on strata grouping of subjects with similar characteristics rather than on matched pairs,[27] and it is also appropriate to include factors not matched in the design stage within the conditioning strata for logistic regression, which allows combined analysis of studies with different matching factors.[28]

Results

On the average, about 25 years of a subject's 32-year residential history was covered by measurements. There were 2,052 residential periods of at least 2 years during the observation period for radon exposure, and radon measurements at corresponding addresses were obtained for 1,595 residential periods (77.7%). The rates for achieving radon measurements were independent of disease status, and this also applies to the reasons for not obtaining measurements (Table 1).

Of the 798 study subjects enrolled (271 lung cancer cases and 527 controls), 745 subjects (258 cases and 487 controls) with at least one address assessed for radon level were included in risk analyses (Table 2). The distribution of these 745 study subjects over number of addresses occupied, and over number of addresses measured, was comparable for cases and controls. The mean period of residence for which direct measurements were available was 26.1 years among case subjects and 26.8 years among control subjects, or 81.7% and 83.8% of the defined exposure period, respectively. Information about risk factors other than radon, obtained through questionnaires, was provided by the subjects themselves (rather than by next-of-kin) for 65.5% of the case subjects and for 76.0% of the controls.

The distributions of cases and controls over the potential confounders, presented in Table 3, suggest differences in risk of lung cancer according to ETS exposure,

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TABLE 1. Outcome of Radon Monitoring in Residential Addresses Occupied by Study Subjects for at Least 2 Years during the 32-Year Period Ending 3 Years before Assessment of Disease Status

	Lung Cancer Cases				Controls			
	Residential Periods		Average Residential Time per Subject		Residential Periods		Average Residential Time per Subject	
Outcome of Measurement Attempt	No.	%	Years	%	No.	%	Years	%
Dwelling with measurement obtained	538	77.1	24.9	80.6	1,057	78.1	24.8	79.6
Dwelling with no measurement obtained								
House no longer in existence	39	5.6	1.5	4.8	73	5.4	1.2	3.9
House not used as residence	39	5.6	1.6	5.2	87	6.4	1.9	6.2
Failure to get in contact with owner	35	5.0	1.3	4.1	66	4.9	1.5	4.9
Failure to locate the house	24	3.4	0.6	1.8	23	1.7	0.4	1.2
Permission for measurement withheld	19	2.7	1.0	3.1	40	3.0	1.1	3.7
House reconstructed	4	0.6	0.1	0.4	6	0.4	0.2	0.5
Damaged detectors	0	0.0	0.0	0.0	2	0.1	0.0	0.0
Total	698	100.0	30.9	100.0	1,354	100.0	31.1	100.0

occupational exposure, and socioeconomic classification. This finding was confirmed in logistic regression analyses stratified for matched factors (age, sex, study center, and matched area of residence) and adjusted for the other risk factors. Except for matching factors, adjustment had very little influence on risk estimates for radon exposure.

TABLE 2. Number of Lung Cancer Cases and Control Subjects for Whom Data on Residential Radon Was Available, According to Study Center, Number of Addresses, and Amount of Residential Time with Measurements

	Cases		Controls	
Characteristic	No.	%	No.	%
Source of data				
Center 1	123	47.7	230	47.2
Center 2	32	12.4	62	12.7
Center 3	34	13.2	65	13.3
Center 4	46	17.8	88	18.1
Center 5	23	8.9	42	8.6
Total	258	100.0	487	100.0
Number of addresses measured				
1	101	39.1	183	37.6
2	76	29.5	147	30.2
3	52	20.2	84	17.2
4–8	29	11.2	73	15.0
Total	258	100.0	487	100.0
Number of addresses*				
1	68	25.1	134	25.4
2	80	29.5	161	30.6
3	58	21.4	111	21.1
4–8	65	24.0	121	23.0
Total	271	100.0	527	100.0
Residential time with measurements available, years†				
2–9.9	15	5.8	29	6.0
10–19.9	40	15.5	54	11.1
20–32.0	203	78.7	404	83.0
Residential time with measurements available, percentage of observation period.				
<25	11	4.3	23	4.7
25–49.9	24	9.3	35	7.2
50–74.9	38	14.7	64	13.1
75–97.9	73	28.3	135	27.7
98–100	112	43.4	230	47.2

* For the original 798 subjects, of which 53 remain without measurement of residential radon concentration.
† Means: cases, 26.1 years; controls, 26.8 years.
‡ Means: cases, 81.7%; controls, 83.8%.

The distribution of TWA radon concentrations among cases was shifted toward higher levels compared with controls, as can be assessed by comparing the group-specific averages and quartiles in Table 4. The contrast between case and control groups with respect to the distribution of TWA radon concentrations was unaffected when gaps in reconstructing the exposure history were imputed with average radon concentrations, although this procedure reduced the variability of the distribution.

We found a trend in the relative risks of lung cancer with increasing radon exposure categories in the current study that is much like the trend shown by the relative risks among never-smokers in the nationwide Swedish study (Table 5). The ERR based on a continuous variable for radon appeared larger in the current study than in the nationwide study. The range of exposure was larger in that study (maximum TWA radon exposure = 2,554 Bq m^{-3}), and there were relatively more controls than cases in the upper range of TWA radon exposures.

Additional analyses evaluated the interaction between residential radon exposure and ETS at home (Table 6). The trend of increased risk with increasing radon levels seems to be limited to subjects exposed to ETS at home, and this pattern was consistent both in the current study as well as among never-smokers in the nationwide study.

Exploratory analyses using only subjects with a large proportion of their observation period for radon exposure covered by actual measurements, or comparing fixed- and random-effect models, did not indicate sensitivity of the present results to these issues. We investigated sensitivity to outliers by restricting the relatively wider range of exposure in the data from the nationwide Swedish study to the range observed in the current study (662 Bq m^{-3}). This analysis changed the ERR per 100 Bq m^{-3} from 0.04 to 0.14, which is closer to the ERR of 0.28 per 100 Bq m^{-3} observed in the current study. For

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the combined data, the ERR was equal to 0.19 per 100 Bq m^{-3} when the range of exposure was restricted, instead of the ERR of 0.10 per 100 Bq m^{-3} when the range was unrestricted. To get an indication as to whether these subjects might be appropriately omitted from regression analyses, we inspected the radon concentrations indicated by the two measuring devices used in each of the 30 dwellings occupied by the 12 study subjects with TWA exposure greater than 662 Bq m^{-3}, but each pair of measurements showed good agreement.

Discussion

The goal of the radon measurement program was to perform measurements in each dwelling occupied by study subjects for at least 2 years during the past 3–35 years. For each single substudy, including never-smokers in the nationwide Swedish study, radon measurements covered at least 78% of the exposure window, which compares favorably with those residential radon studies for which the exposure window covers about three decades. Although lack of measurement for some dwellings cannot be avoided, it is important that the failure rates should be similar for the case group and the control group, because lack of measurement could be related to radon levels. Furthermore, bias would be more plausible if reasons for lack of measurement differed between the two groups of subjects. None of this was apparent in the present study, either when dwellings were taken as a unit for assessment or when the units were the subjects.

The radon levels observed in the new data are lower than in the never-smoker data from the nationwide Swedish study in which the arithmetic mean for TWA radon concentrations was 108 Bq m^{-3} (111 Bq m^{-3} for cases, 107 Bq m^{-3} for controls). The percentages of TWA radon concentrations that exceeded the levels of 200 and 400 Bq m^{-3} in these two datasets were 4.8% and 0.8% for the current data and 9.6% and 2.0% for never-smokers in the nationwide Swedish study. In that study, subjects were selected from municipalities likely to be either low- or high-radon areas, which explains the greater representation of higher radon exposure levels. The relative risks obtained in the present reanalysis were slightly different from those previously published, as the imputation method was different and the length of the exposure window slightly shorter,[20] which also explains why there were two subjects from that study who had no dwelling measured during the observation period for radon exposure in the present analysis.

The ERR of 0.10 per 100 Bq m^{-3} observed in the present study for all subjects combined is consistent with the ERR of 0.12 at 100 Bq m^{-3} TWA radon concentration (95% confidence limits of about −0.15 and 0.4) produced in a previous meta-analysis of nonsmokers from five residential studies that included 777 never-smoker and 161 longtime former-smoker cases (the ERR is also consistent with the overall results for smokers and nonsmokers combined from pooled residential studies or pooled miner studies).[4,5,8,20,29–32] The ERR from the meta-analysis of nonsmokers was mostly driven by the results from a single study.[5]

Miner studies have reported a positive interaction between radon and smoking that is less than multiplicative, because the radon-related ERR was greater for never-smokers than for smokers.[4,8,33] The study of interactions generally requires more statistical information than main analyses, and although miner studies benefit from a wide range of exposure, there were few cases of lung cancer (a total of 64) among never-smokers.[4,8] The ten epidemiologic studies of residential radon conducted so far in the general population, with a minimum of 200 subjects and long-term radon measurements in at least one of the subjects' dwellings, include a total of about 900 never-smoker cases of lung cancer.[20,29–32,34–38] In contrast to the findings among miners, the ERRs among smokers tend to be larger than among never-smokers, in residential radon studies in which such comparison is possible,[20,29,31,32,34,35,38] with possibly an exception for a

TABLE 3. Characteristics of Lung Cancer Cases and Control Subjects Available for Risk Analyses

Characteristic	Cases No.	Cases %	Controls No.	Controls %
Sex				
Male	114	44.2	220	45.2
Female	144	55.8	267	54.8
Age, years*				
28–54	36	14.0	72	14.8
55–64	50	19.4	92	18.9
65–74	98	38.0	181	37.2
75–94	74	28.7	142	29.2
Resident 10 years or more in urban centers				
Yes	127	49.2	240	49.3
No	131	50.8	247	50.7
Environmental tobacco smoke at home				
Time since last exposure, years:				
Less than 3	19	7.4	33	6.8
3–15	28	10.9	52	10.7
15 or more	48	18.6	81	16.6
Unknown	5	1.9	9	1.8
Unexposed	155	60.1	306	62.8
Unknown	3	1.2	6	1.2
Occupational lung cancer risk (List A)†				
Yes	12	4.7	17	3.5
No	240	93.0	463	95.1
Unknown	6	2.3	7	1.4
Occupational lung cancer risk (List B)‡				
Yes	27	10.5	44	9.0
No	225	87.2	436	89.5
Unknown	6	2.3	7	1.4
Socioeconomic indicator				
Shorter education and manual work	85	33.0	148	30.4
Shorter education and nonmanual work	63	24.4	104	21.4
Longer education and manual work	46	17.8	92	18.9
Longer education and nonmanual work	58	22.5	136	27.9
Unknown	6	2.3	7	1.4
Cell type (by sex)	Women		Men	
Adenocarcinoma	85	59.0	59	51.8
Squamous	16	11.1	20	17.5
Small cell	4	2.8	11	9.7
Other	39	27.1	24	21.1

* Means: cases, 68.0 years; controls, 68.0 years.
† Occupations recognized to present lung cancer excess risk.[12,13]
‡ Occupations suspected to present lung cancer excess risk.[12,13]

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TABLE 4. Distribution of Time-Weighted Average (TWA) Residential Radon Concentrations, by Disease Status,* When Estimates Are Based on Measured Concentrations Only, and When Time Periods in the Residential History That Are Not Covered by Radon Measurements Are Replaced by Imputed Values

TWA Radon Concentration (Bq m^{-3})	Cases		Controls	
	No.	%	No.	%
Based on measured radon concentrations, ignoring unmeasured residential periods				
≤25	42	16.3	75	15.4
26–50	70	27.1	145	29.8
51–100	72	27.9	146	30.0
101–200	57	22.1	93	19.1
201–400	14	5.4	23	4.7
>400	3	1.2	5	1.0
Total	258	100.0	487	100.0
Arithmetic mean†	86		79	
Quartiles†	33,60,115		32,56,100	
Minimum†	2		7	
Maximum†	552		662	
With imputation for unmeasured residential periods‡				
≤25	17	6.6	41	8.4
26–50	71	27.5	137	28.1
51–100	102	39.5	192	39.4
101–200	55	21.3	94	19.3
201–400	10	3.9	20	4.1
>400	3	1.2	3	0.6
Total	258	100.0	487	100.0
Arithmetic mean†	87		80	
Quartiles†	42,65,106		41,62, 98	
Minimum†	2		7	
Maximum†	552		662	

* Using lung cancer cases and control subjects with at least one dwelling measured for radon during the 32-year period ending 3 years prior to assessment of disease status.
† Bq m^{-3}.
‡ See Subjects and Methods for a description of the imputation procedure for residential periods without radon measurements.

study in Stockholm, Sweden, in which interpretation is complicated by sensitivity of the results to the choice of a categorical or continuous radon exposure variable for analyses.[30,39] An assessment of heterogeneity of ERR by ETS status was done here for the first time in a radon study, and an interaction that is at least multiplicative between ETS and radon was suggested. As discussed above, this would be in line with the type of interaction observed between radon and smoking in residential studies, but it may be specific to residential radon levels and not applicable over the entire range of exposure found in miner studies.

Contemporary measurements of radon concentrations were used to represent concentrations up to four decades

TABLE 5. Relative Risk (RR) of Lung Cancer by Levels of Average Radon Concentration in Residential Addresses Occupied by Study Subjects during the 32-Year Period Ending 3 Years before Assessment of Disease Status

	Category of Radon Concentration* (Bq m^{-3})																
	≤50†			50–80				80–140				>140RR95% CL					
Source of Subjects	Cases	Controls	RR‡	Cases	Controls	RR	95% CI	Cases	Controls	RR	95% CI	Cases	Controls	RR	95% CL	Excess RR per 100 Bq m^{-3}‡§	
Current study	88	178	1.0	77	146	1.03	0.67–1.57	56	112	1.14	0.72–1.81	37	51	1.55	0.88–2.73	0.28	−0.05,1.05
Never-smokers in the previous nationwide Swedish study	42	306	1.0	43	290	1.18	0.75–1.88	56	364	1.24	0.80–1.92	37	202	1.44	0.87–2.35	0.04	<−0.04,0.35
Current smokers and never-smokers in the nationwide Swedish study	130	484	1.0	120	436	1.08	0.79–1.47	112	476	1.18	0.86–1.61	74	253	1.44	1.00–2.06	0.10	<−0.04,0.38

95% CL = 95% confidence limits; ERR = excess relative risk.
* Radon concentration for each address weighted in proportion to the length of time for which the subject lived there, with missing values imputed using study-specific average radon concentrations in addresses of control subjects.
† Reference category.
‡ Relative risk after stratification on study; sex; age group; matched area of current residence; and adjustment for passive smoking, urbanization, occupational lung cancer risk, and socioeconomic status.
§ The sign "<" indicates that the likelihood had not yet decreased by a sufficient amount to correspond to a 97.5% likelihood-based confidence limit as the excess relative risk reached the minimum value that could be produced by the model (the product of a negative excess relative risk and the maximum exposure value should not be smaller than −1 to ensure a nonnegative relative risk).

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TABLE 6. Relative Risk (RR) of Lung Cancer According to Smoking Habits of Spouse and Levels of Average Radon Concentration in Residential Addresses Occupied by Study Subjects during the 32-Year Period Ending 3 Years before Assessment of Disease Status (Combining Current Study Subjects and Never-Smokers in the Previous Nationwide Swedish Study)

ETS at Home	Category of Radon Concentration* (Bq m^{-3}) ≤50 Cases	≤50 Controls†	≤50 RR‡	50–80 Cases	50–80 Controls	50–80 RR	50–80 95% CI	80–140 Cases	80–140 Controls	80–140 RR	80–140 95% CI	>140 Cases	>140 Controls	>140 RR‡	>140 95% CL§	ERR per 100 Bq m^{-3}‡§
Yes	45	195	1.0‖	48	152	1.43	0.86–2.36	51	167	1.76	1.08–2.86	35	97	2.10	1.21–3.65	0.29	−0.03,1.24
No	83	278	1.0‖	72	274	0.93	0.63–1.38	60	296	0.88	0.58–1.34	39	149	1.13	0.70–1.82	0.02	<−0.06,0.32

ETS = environmental tobacco smoke; ERR = excess relative risk.

* Radon concentration for each address weighted in proportion to the length of time for which the subject lived there, with missing values imputed using study-specific average radon concentrations in addresses of control subjects.

† Three cases and 41 controls for which no information on ETS was available were excluded.

‡ Relative risk, or excessive relative risk, after stratification on study; sex; age group; matched area of current residence; and adjustment for urbanization, occupational lung cancer risk, and socioeconomic status.

§ The sign "<" indicates that the likelihood had not yet decreased by a sufficient amount to correspond to a 97.5% likelihood-based confidence limit as the excess relative risk reached the minimum value that could be produced by the model (the product of a negative ERR and the maximum exposure value should not be smaller than −1 to ensure a nonnegative RR.

‖ Reference category.

ago. Preceding work suggests that the ERR estimates are likely to be underestimated owing to random error in exposure estimates; in Swedish studies underestimation by a factor of nearly 2 is probable,[40,41] and a comparably large impact on the risk estimates has subsequently been shown to hold for a residential radon study in south-west England.[34] Additional bias could occur if 3-month measurements during the heating season overestimated yearly concentrations, although preliminary results from work in progress show that the effects are probably small.

Omitting subjects with the largest amount of imputation from analysis had little consequence on the ERR estimate, as most subjects had a very large proportion of their observation period for radon exposure covered by actual measurements. By contrast, excluding subjects with large radon exposure values tended to increase the ERR. The main contributor to random error in exposure estimation is the variation in radon concentrations over calendar years in the same dwelling,[41] and therefore the agreement verified between the readings from the two detectors in each dwelling of these subjects, which rules out a measurement error, does not preclude imprecision in exposure assessment. Because large estimated exposures on the average correspond to smaller true exposures and induce downward curvature in a true linear exposure response,[41] an increase in the ERR estimate may be expected after exclusion of such subjects.

In conclusion, the present study adds to the limited data on radon exposure and lung cancer in never-smokers. Overall, the radon-related ERR of lung cancer among never-smokers does not appear to depart much from that in smokers (but is obviously much smaller in terms of absolute excess risk). Among never-smokers, residential radon exposure may be more harmful for those exposed to ETS.

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